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(71) Applicant *(for all designated States except US)*: A.B. TECHNOLOGIES, L.L.C. [US/US]; 852 Redgate Road, Dresher, PA 19025–1431 (US).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: SCHMIDT, William, J. [US/US]; 852 Red Gate Road, Dresher, PA 19025–1431 (US).

(74) Agent: KIPNES, Allen, R.; Watov & Kipnes, P.C., P.O. Box 247, Princeton Junction, NJ 08550 (US).

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(54) Title: MULTI CHAMBER SOFT CAPSULES AND METHOD OF MAKING THE SAME

(57) Abstract

Soft capsules having a plurality of subchambers separated by a barrier material which is at least substantially non–permeable to the active agents contained within the subchambers are disclosed. Apparatus and method of making the soft capsules are also disclosed.

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Field Of The Invention

The present invention is directed to soft capsules, typically gelatin capsules, which are used to encapsulate a wide variety of products including pharmaceutical, nutritional, neutraceutical, cosmetic, cosmeceutical, food, and fertilizer products, and the like. The capsule contains at least two chambers which are separated from each other by a substantially impermeable barrier so that different substances may be encapsulated within the separate chambers.

Background Of The Invention

Protein and protein-like materials, especially gelatin and gelatin derivatives are used to encapsulate the products produced in several industries. Examples of gelatin and derivatives thereof and the formation of capsules therefrom are described in Simpson et al., U.S. Patent No. 5,074,102 which is incorporated herein by reference. Such capsules can be used to encapsulate medicinal compounds such as drugs or vitamins; as a food packaging mechanism for packaging food products such as powdered instant coffee or spices; in candy manufacturing; in fertilization of plants by encapsulation of fertilizers, in packing of sensitive seeds in combination with protective agents and/or fertilizers; and in the packaging of single dyestuffs or mixtures thereof. More recently such capsules have been used for nutritional, neutraceutical, cosmetic and cosmetical encapsulated ingredients as well. Such capsules are limited to the

encapsulation of a single substance or compatible substances because the capsule itself has but a single chamber for storage of the active ingredient.

Some capsules have been designed to provide for multiple dosage units. For example, Goodheart et al., U.S. Patent No. 5,074,426 discloses a capsule which is divisible into accurate individual dosage units for administering a medicine. The capsule is easily separated by pulling it into capsule units. The capsule comprises a first and second capsule unit, each for holding a desired medicinal preparation. The first and second capsule units are of cylindrical shape and have a longitudinal axis. The first and second capsule units have first and second ends wherein the first ends are rounded and the second ends are sealed by a closure. The closures of the respective capsule units abut each other and are detachably joined to each other.

Another such multiple dosage capsule is disclosed in Makiej, U.S. Patent Nos. 4,793,493 and 4,936,461. These references disclose multiple dose capsules that may be broken into separately administratable dosages. The hard gelatin capsule comprises a longitudinal tube with a dividing section between respective first and second ends. The tube has a severable portion relative to first and second walls.

Nugent, U.S. Patent No. 4,601,896 discloses a pharmaceutical capsule for oral administration of gastric-sensitive therapeutic agents. The capsule has an outer housing made from a gastric-fluid impervious composition in which the housing contains

a first chamber containing a gastric sensitive therapeutic agent and a second chamber containing an activator material capable of dissolving the capsule. Prior to taking the capsule, the patient applies pressure to the capsule to rupture the second chamber thereby releasing the activator which dissolves the capsule in a predetermined time thereby releasing the gastric sensitive therapeutic agent in the patient's intestinal tract.

Soft gelatin capsules are a desirable oral dosage form because they are easy to swallow and are readily digestible. They also provide an adequate encapsulation of a therapeutically active agent with often prompt release in the gastrointestinal tract. However, it is often desirable for a patient to receive two or more active agents, which may not be compatible with each other (e.g. may react with each other) in a manner which irreversibly changes at least one of the active agents.

It would therefore be a significant benefit in the art to provide a soft capsule, such as a soft gelatin capsule, which enables the administration of two or more materials (e.g. active agents) at the same time.

It would be a further significant benefit in the art to provide a soft capsule which contains at least two chambers or compartments which are separated by a substantially non-permeable barrier so that the different materials contained within the separated compartments cannot adversely affect each other during storage or administration of the capsule.

Summary Of The Invention

The present invention is generally directed to a soft capsule typically made out of gelatin or derivatives thereof having a chamber subdivided into at least two subchambers. The subchambers are separated from each other by a barrier which is substantially impermeable to the contents of the respective subchambers. In particular, the present invention is directed to

a soft capsule for housing at least one agent comprising:

a) a chamber; and

b) at least one barrier dividing the chamber into at least two subchambers, said barrier being at least substantially non-permeable to the at least one agent.

In a preferred form of the invention, the barrier comprises a membrane which is at least substantially non-permeable to the contents of the subchambers.

In another aspect of the present invention, there is provided a method of forming a soft capsule having a chamber subdivided into at least two subchambers by the barrier as described above. In a particular aspect of the invention the method comprises passing at least one ribbon of a material which is at least substantially non-permeable to said at least one agent between opposed ribbons of a soft capsule-forming material at a temperature and under pressure sufficient to produce a soft

capsule having at least two subchambers separated by a barrier of said substantially non-permeable material.

Brief Description Of The Drawings

The following drawings in which like reference characters indicate like parts are illustrative of embodiments of the invention and are not intended to limit the invention as encompassed by the claims forming part of the application.

Figure 1 is schematic view of an apparatus for forming soft capsules having a chamber subdivided into two subchambers in accordance with the present invention;

Figure 2 is a cross-sectional view of an embodiment of a dual subchamber soft capsule formed by the apparatus shown in Figure 1; and

Figure 3 is a cross-sectional view of another embodiment of a dual chamber soft capsule formed by the apparatus shown in Figure 1.

Detailed Description Of The Invention

The making of soft capsules especially soft gelatin capsules is well known in the art. Methods for producing soft gelatin capsules are disclosed for example in U.S.

Patent No. 5,074,102 and references cited therein including U.S. Patent No. 4,655,027, U.S. Patent No. 4,817,367 and U.S. Patent No. 2,775,267, each of which is incorporated herein by reference.

The employment of ribbons of soft gelatin material to form a soft gelatin capsule through the pressure exerted by opposed rotatable dies is well known. In accordance with the present invention, at least one additional ribbon of an additional material, preferably at least a substantially non-permeable material as hereinafter described is placed between the opposed ribbons of the soft gelatin material. The additional material is one which is at least preferably substantially non-permeable to the agents contained within the subchambers. As used herein the term "at least substantially non-permeable" shall mean a material which does not allow passage of an agent contained within a subchamber into another subchamber to the extent that the function and/or structure of the agent is adversely affected. The additional material provides at least a substantially non-permeable barrier dividing the soft gelatin capsule into at least two subchambers in which the contents of the respective subchambers do not permeate into any other subchamber to the detriment of any one of the agents contained with the subchambers.

The substantially non-permeable material as defined herein and which is used to provide a barrier between subchambers will vary depending on the type of agents that are contained within the subchambers. The selection of a suitable substantially

non-permeable material is within the skill of the art. However, a preferred embodiment of the invention is to employ the same material as used to form the soft capsule since the soft capsule material is typically selected to be generally at least substantially non-permeable to the agents contained within the subchambers. Thus, if the capsule is made of gelatin, the barrier material may be made by gelatin or derivatives thereof. The barrier material can be made from, in addition to soft gelatin, such materials as cellulose and derivatives thereof, lipids and derivatives thereof, polyols and derivatives thereof, starches and derivatives thereof and the like. The selection of a suitable barrier material will, of course, depend in part on the agents which are to be contained within the subchambers. In accordance with the present invention, the barrier material should be at least substantially non-permeable to the agents if there mixing together would adversely affect at least one of the agents.

Referring to Figure 1, there is shown a portion of the capsule forming apparatus employed in the present invention which brings together the respective ribbons of material to form the capsules of the present invention having at least two subchambers. Other portions of the capsule forming apparatus which are not shown are known and within the skill of the art.

In particular, the present invention provides for a split wedge comprised of a left wedge 8 and a right wedge 9. The split wedge is situated above a nip created between a pair of opposed rotatable die rolls, a left die roll 13 and a right die roll 14, which rotate

in opposite directions. In the particular embodiment shown in Figure 1, the left die roll 13 is rotating in a clockwise direction and th right die roll 14 is rotating in a counterclock direction.

A first or left ribbon 6 of soft material, for example, soft gelatin material is fed between the left wedge 8 and the left die roll 13. A second ribbon or right ribbon 7 of soft gelatin material is fed between the right wedge 9 and the right die roll 14.

In accordance with the present invention, a third ribbon or central ribbon 1 of a barrier material such as a soft gelatin material is fed between the left wedge 8 and the right wedge 9.

Rotation of the respective left and right die rolls 13 and 14 thereby creates the formation of a multi-chamber soft gelatin capsule 15.

The filling of the left and right subchambers 23a and 23b of the soft gelatin capsule (see Figures 2 and 3) is accomplished by feeding a first substance "A" through a right injection lead 4 and simultaneously feeding a second substance "B" through a left injection lead 5 to the nip as the die rolls 13 and 14 rotate and the multi-chamber capsules 15 are being formed. The gelatin ribbons 1, 6 and 7 are delivered to the left and right die rolls 13, 14 such that the gelatin ribbons are drawn into the nip from both sides as the die rolls 13, 14 rotate. Pumps (not shown) control injection leads 4 and 5

via left and right shut-off valves 2 and 3 and will, therefore, operate simultaneously to achieve the simultaneous filling of subchambers 23a and 23b with an agent such as a pharmaceutical, vitamin or the like.

Each die roll 13, 14 is formed with a plurality of hemispherical recesses 12 defined at the die roll surface by cutting edges or surfaces 20. In use, the die rollers 13, 14 rotate in synchrony with each other such that the recesses 12 are in registry at the nip, and with injection leads 4 and 5. As a result, the fill material is injected between ribbons 1 and 6 and 1 and 7 when they are respectively located over the juxtaposed recesses 12. The injected fill material forces ribbons 6 and 7 away from central ribbon 1 into the respective recess 12 until the capsule is closed by the coming together of the cutting edges and surfaces 20. Multi-chamber capsules 15 are thus produced sequentially with a length of laminated gelatin netting 19 therebetween. The cutting edges and surfaces 20 separate the gelatin netting 19 from the capsules 15 so that the capsules are produced individually.

In rotary die encapsulation machines of the kind illustrated in Figure 1, each die roll will normally have sufficient axial length to have a substantial number or recesses raised along its width. As a consequence, whereas the capsules 15 are produced individually, the laminated ribbon 19 takes the form of a perforated sheet which is drawn away as waste or recycled.

The apparatus of Figure 1 includes left and right wedge heaters 10 and left and right temperature probes 11 to maintain proper temperature control during capsule formation and filling.

Once the multi-chamber capsule 15 is formed it is separated from the laminated gelatin ribbons 19 via a chute assembly 16. The present invention also illustrates left and right flippers 17 to dislodge capsule material that has not discharged from the die rolls 13 and 14.

The multi-chamber capsule forming mechanism described above in Figure 1 can be applied to filled capsules containing, but not limited to, liquids, semi-solids and, powders and particulates with some modification to the mechanism of capsule formation as discussed in U.S. Patent 5,740,660, incorporated herein by reference.

Embodiments of soft capsules produced in accordance with the present invention are shown in Figure 2. Referring to Figure 2, a capsule 30 is comprised of an outer shell 21 formed from the respective ribbons 6 and 7 discussed above in connection with Figure 1. A barrier 22 is formed from the ribbon 1 which is comprised of a substantially non-permeable material discussed above in connection with Figure 1. The barrier 22 divides the capsule 30 into two subchambers 23a and 23b. Each of the subchambers 23a and 23b can contain a separate agent even if the active agents are incompatible with each other since the barrier 22 prevents one agent from

contacting the other to the extent that neither of the agents are adv rsely affected with respect to structure and function.

A further embodiment of a soft capsule is shown in Figure 3. This embodiment is similar to the embodiment of Figure 2 except that it includes a twist off seal 24. Such capsules are particularly useful for topical applications and personal care products.

It will be understood that the capsule can contain a plurality of subchambers by adding additional ribbons of material as discussed above in connection with Figure 1. Thus, capsules containing three or more subchambers may be constructed within the spirit and scope of the present invention.

The capsules of the present invention can be used to house a wide variety of incompatible as well as compatible agents including, but not limited to pharmaceutical, nutritional, nutraceutical, cosmetic and cosmeticeutical. The contents of the subchambers as contemplated in the present invention include, but are not limited to, active agents such as prescription and non-prescription medications, drugs and the like, cosmetics, nutrients, vitamins, neutraceuticals, and the like. The subchambers can also include one or more non-active agents such as emulsifiers, pH indicators, esterifiers, surface active agents and the like.

By way of example, a dual subchamb r capsule can contain two different active agents (e.g. an antihistamine and a vitamin complex), the same active agent in different phases (e.g. a solid phase in one subchamber for slow release and a liquid phase in another subchamber for rapid release of the active agent), two agents which react together to form a desired active agent through chemical reaction such as hydrolysis, oxidation, esterification, salt formation and the like, oil-aqueous phase agents such as oil soluble vitamins in one subchamber and water-soluble vitamins in another subchamber. These represent but a few of the possible combinations which may be employed in capsules prepared in accordance with the present invention.

The capsules prepared in accordance with the present invention can be used for internal applications as illustrated above and for external or topical applications. For example, a capsule can contain a hair relaxing formulation typically including an alkaline component and a hair treating emulsion formation in another subchamber. In another example, a vitamin C emulsion can be used in one subchamber while an alpha-hydroxy acid formulation having a relatively low pH can be placed in another subchamber.

It will be understood in accordance with the present invention that gelatin and derivatives thereof are the most common soft capsule forming materials. It will be appreciated that other soft capsule forming materials may be employed within the spirit and scope of the present invention.

What Is Claimed:

1. A soft capsule for housing at least one agent comprising:

a) a chamber; and

b) at least one barrier dividing the chamber into at least two subchambers, said barrier being at least substantially non-permeable to the at least one agent.

2. The soft capsule of claim 1 wherein the capsule comprises at least one material selected from the group consisting of gelatin, cellulose, lipids, polyols, starch and respective derivatives thereof.

3. The soft capsule of claim 1 comprising more than two subchambers.

4. The soft capsule of claim 1 wherein the barrier comprises at least one material selected from the group consisting of gelatin, cellulose, lipids, polyols, starch and respective derivatives thereof.

5. The soft capsule of claim 4 wherein the barrier comprises gelatin or a derivative thereof.

6. A method of forming a soft capsule for housing at least one agent, said method comprising passing at least one ribbon of a substantially non-permeable

material betwe n opposed ribbons of a soft material to produc a soft capsule having at least two subchambers separated by a barrier of said substantially non-permeable material.

7. The method of claim 6 wherein the opposed ribbons comprise gelatin or a derivative thereof.

8. The method of claim 6 comprising passing a plurality of ribbons of a substantially non-permeable material between said opposed ribbons to produce a soft capsule having more than two subchambers.

9. The method of claim 6 wherein the substantially non-permeable material is selected from the group consisting of gelatin, cellulose, lipids, polyols, starch and respective derivatives thereof.

10. The method of claim 9 wherein the substantially non-permeable material is gelatin or derivatives thereof.

11. Apparatus for the formation of a soft capsule comprising:

a) first soft material delivery means for delivering a first soft capsule material between a first wedge and a first roller;

b) second soft material delivery means for delivering a second ribbon of soft capsul material between a second wedge and a second roller;

c) at least one barrier material delivering means for delivering a barrier material between said first and second wedges, said barrier material being substantially non-permeable to any agent contained within the capsule, said barrier material dividing the capsule into at least two subchambers; and

d) active agent delivering means for delivering at least one active agent to at least one of said subchambers.

12. The apparatus of claim 11 wherein the first and second soft capsule materials are selected from the gelatin, cellulose, lipids, polyols, starch and derivatives thereof.

13. The apparatus of claim 11 wherein the barrier material(s) is selected from the group consisting of gelatin, cellulose, lipids, polyols, starch and derivatives thereof.

14. The apparatus of claim 13 wherein the barrier material is gelatin or a derivative thereof.

15. The apparatus of claim 11 wherein the barrier material is the same material as at least one of the first and second capsule materials.

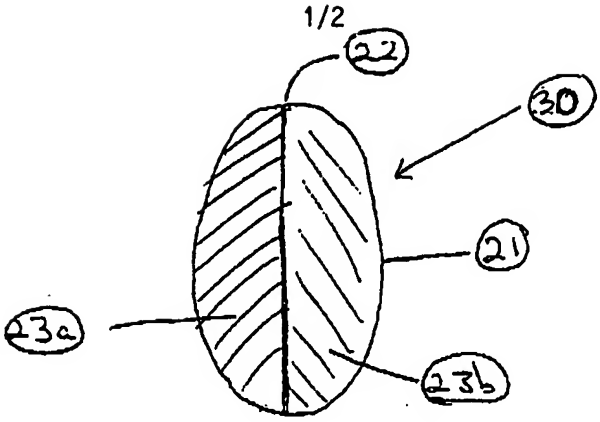

Figure 2

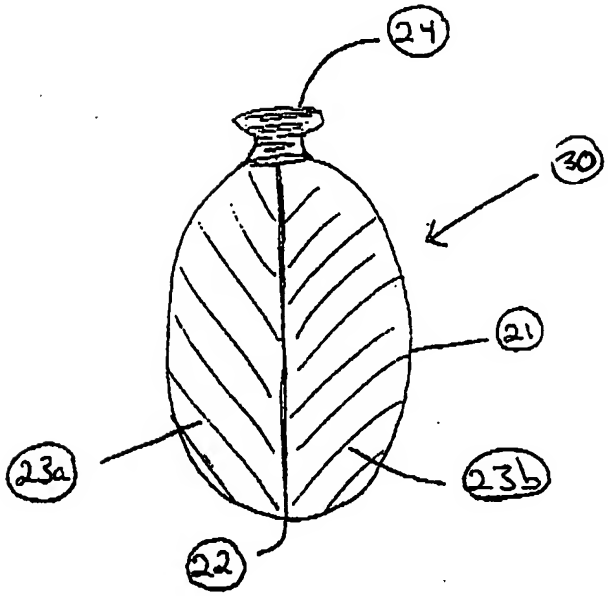

Figure 3

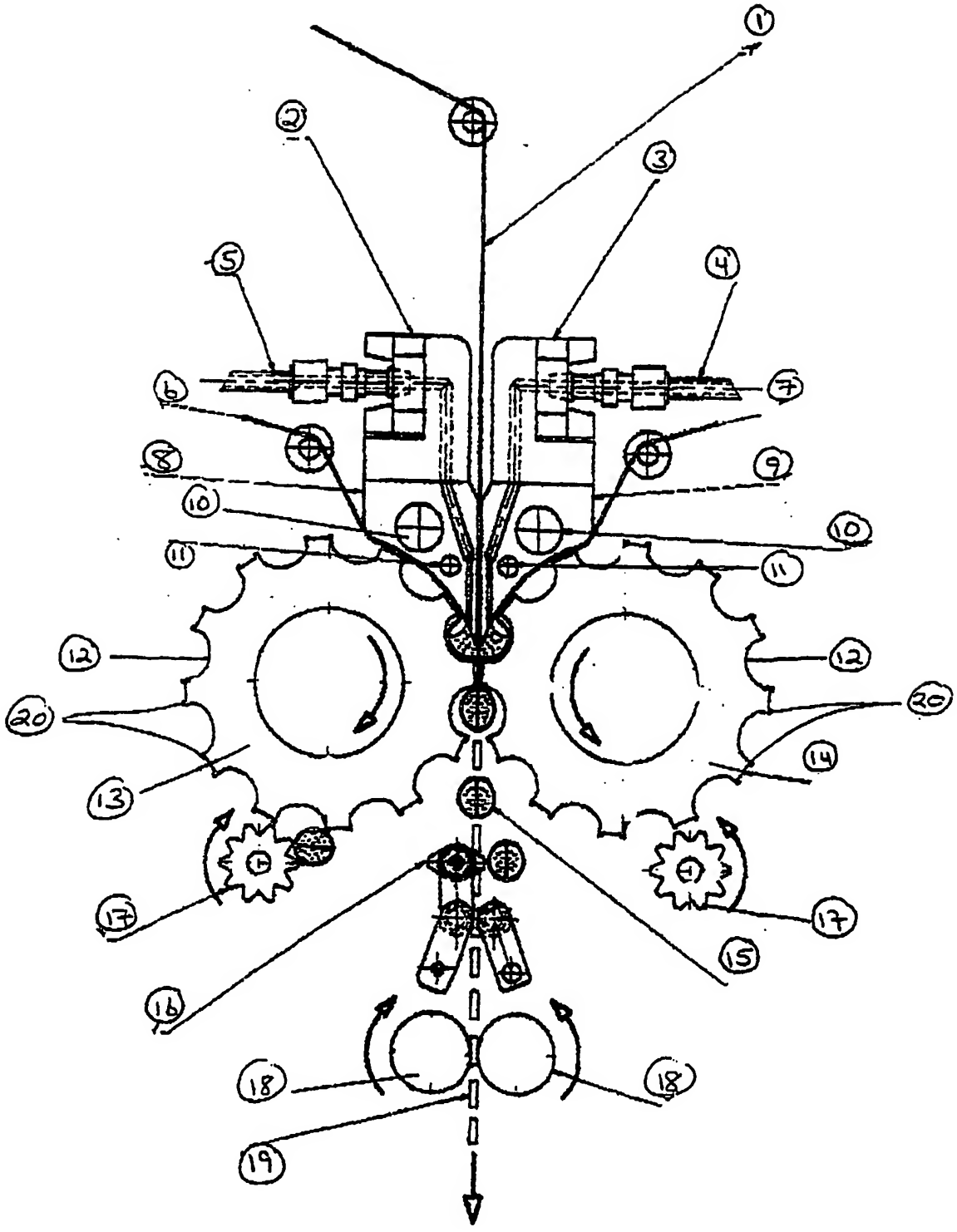

FIGURE 1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/27093

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :A61K 9/48
US CL :424/451, 452, 454, 456

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/451, 452, 454, 456

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WEST search terms: capsule, gelatin, barrier, membrane, ribbon, multidose, chamber, cellulose, starch, divide, third, compartment, section, semipermeable, section

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 3,732,865 A (HIGUCHI et al) 15 May 1973, see figure 3, column 6, lines 25-68, column 7, lines 30-50, column 8, lines 40-56, claim 1.	1, 2, 4, 5
Y	US 4,936,461 A (MAKIEJ, Jr.) 26 June 1990, see entire document.	1-10
A	US 5,740,660 A (ROWE) 21 April 1998, see entire document.	1-15

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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